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Imidazole Derivatives as a Novel Class of Hybrid Compounds with Inhibitory Histamine *N*-Methyltransferase Potencies and Histamine hH_3 Receptor Affinities

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Abstract—In this study, a novel series of imidazole-containing compounds with dual properties, that is, inhibitory potency at the enzyme histamine N^{τ}-methyltransferase (HMT) and antagonist potency at histamine H_3 receptors was designed and synthesized. Pharmacologically, these new hybrid drugs were evaluated in functional assays for their inhibitory potencies at rat kidney HMT and for their antagonist activities on synaptosomes of rat cerebral cortex. For selected compounds, binding affinities at recombinant human histamine H_3 receptors were determined. The first compounds (**1**–**10**) of the series proved to be H_3 receptor ligands of high potency at rat synaptosomes or of high binding affinity at human H_3 receptors, respectively, but of only moderate activity as inhibitors of rat kidney HMT. In contrast, aminoquinoline- or tetrahydroacridine-containing derivatives **11**–**17** also displayed HMT inhibitory potency in the nanomolar concentration range. Preliminary data from molecular modeling investigations showed that the imidazole derivative **15** and the HMT inhibitor quinacrine possess identical binding areas. The most interesting compound (**14**) is simultaneously a highly potent H_3 receptor ligand ($K_i = 4.1$ nM) and a highly potent HMT inhibitor ($IC_{50} = 24$ nM), which makes this derivative a valuable pharmacological tool for further development.

Introduction

Endogenous histamine does not only play a role in the immediate allergic response and in the regulation of gastric acid secretion, but does also function as a neurotransmitter in the peripheral and mainly in the central nervous system (CNS).[1,2] In neurons within the CNS, histamine is physiologically synthesized from its precursor L-histidine by cytoplasmatic L-histidine decarboxylase (E.C. 4.1.1.22), stored vesicularly and released from terminals in a calcium-dependent mechanism.[3] In contrast to other aminergic neurotransmitters, there is no high-affinity reuptake system detected so far for its removal from the synaptic cleft, but an enzymatic inactivation occurs in the neighbouring glia cells.[3] In mammalian tissues, two major pathways of histamine metabolism exist depending on species and organ localization.[4] Histamine itself shows only a low affinity for monoamine oxidases A (MAO-A) and B (MAO-B).[5] However, in the periphery, histamine undergoes oxidative deamination catalyzed mainly by the non-specific enzyme diamine oxidase (DAO, E.C. 1.4.3.6) resulting in the products imidazole acetic acid and, eventually, its corresponding riboside.[5] Alternatively and more importantly in the CNS, histamine is inactivated by the ubiquitously distributed enzyme histamine *N*-methyltransferase (HMT,

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E.C. 2.1.1.8) by methylation in the N^{τ}-position of the imidazole ring.[3] *S*-Adenosyl-L-methionine functions as the methyl donor.[2] Most of the product, N^{τ}-methylhistamine, is converted by either DAO (in the periphery) or MAO-B (E.C. 1.4.3.4, in the CNS) into the corresponding aldehyde which is finally transformed into (N^{τ}-methylimidazol-4-yl)acetic acid by special oxidases.[3] All metabolites have little or no activity at histamine receptor subtypes and are excreted in the urine.[5] In the CNS, the methylation of histamine by HMT appears to be the sole pathway since the oxidatively deaminating DAO is absent.[5,6] Moreover, because the resulting catabolite N^{τ}-methylhistamine is inactive at the different types of histamine receptors,[7] the process of methylation by HMT appears to be the crucial step for the inactivation of histamine in the CNS. For in vivo quantification of H_3 receptor-dependent brain activation or inactivation the N^{τ}-methylhistamine level can be applied as measurement.

At present, four different types of histamine receptors (H_1–H_4) are known which all belong to the superfamily of G-protein coupled receptors.[8,9] The recent cloning and characterization of the histamine H_3 receptor in human,[10] rat,[11] mouse[12] and guinea-pig[13] quickly led to considerable information regarding species differences, expression pattern, receptor subtypes, constitutive activity, and pharmacological response.[14] The histamine H_3 receptor, located presynaptically in histaminergic and non-histaminergic neurons,[1] is highly expressed in the CNS and, when recombinantly expressed, couples to inhibition of adenylyl cyclase presumably through $G_{\alpha i}$.[10] Stimulation of H_3 receptors modulates the synthesis and release of several monoaminergic and peptidergic neurotransmitters such as histamine,[15] glutamate, noradrenaline, serotonin, acetylcholine, and substance P.[8]

Blockade of histamine H_3 autoreceptors by antagonists interrupts a negative feedback mechanism and leads to increased histamine levels. Predominantly localized in the brain,[7] histamine H_3 receptors interact with a variety of different signal transduction mechanisms and mediate important (patho)physiological processes, for example, arousal and mood control.[2] For antagonists of histamine H_3 receptors several therapeutic targets have been proposed. Most promising seems to be their application as cognition enhancers, e.g., in Alzheimer's disease,[16,17] in attention-deficit hyperactivity disorder[18] as well as in memory and learning deficits.[19]

Systemic administration of potent inhibitors of HMT also results in significantly increased histamine concentrations in the brain, especially in combination with a histamine H_3 receptor antagonist.[20] Since HMT is highly specific for its substrate histamine,[5] this appears to be a novel strategy for the selective regulation of histaminergic neurotransmission. Hybrid compounds combining both H_3 receptor antagonist properties and HMT inhibitory activities in one molecule could also contribute to the elevation of extracellular histamine levels in the CNS by additional or synergistic effects. In contrast to the combined application of two compounds these new agents are advantageous because of single pharmacokinetics and toxicology. Thus, they represent a novel class of drugs with a dual mode of action which might be useful pharmacological tools as well as potential drugs in psychiatric and neurodegenerative diseases.

Very recently, our group has reported on the first series of compounds which actually combine both pharmacological profiles in one molecule.[21] A systematic structure–activity survey resulted in the discovery of FUB 854 (chart 1), a potent non-imidazole histamine H_3 receptor antagonist ($K_i = 19$ nM) and highly active HMT inhibitor ($IC_{50} = 34$ nM).[21]

In the light of this preceding work we wish to describe our findings in the area of imidazole-containing derivatives. Our objective herein is to determine whether the combined pharmacological action (H_3 receptor antagonism and HMT-inhibition) that is observed for piperidine-containing compounds of the FUB 854-type can be extended to the imidazole class. An imidazole moiety is also an integral part of the most potent H_3 receptor antagonists and seems to be one important element responsible for histamine H_3 receptor binding. In addition, these compounds are of special interest as they show a closer structural relationship to histamine, the endogenous agonist and the HMT substrate. The second part of the molecule is presumed to affect HMT inhibition. We here report on design, synthesis, and pharmacological evaluation of numerous imidazole derivatives in which this moiety is linked by an alkyl or alkenyl spacer to an additional aromatic heterocycle or carbocycle. Antimalarial drugs like amodiaquine[22] or quinacrine[23] (Chart 1) are among the strongest inhibitors of HMT described so far ($K_i = 0.01$–$0.1\ \mu$M). Because of the differences in the test systems applied (different enzyme purities, organs, species, etc.) a direct comparison of these pharmacological data with those described in this article is difficult. In this context, it should also be mentioned that the antidementia drug tacrine[24] (Chart 1) in therapeutically relevant concentrations potently inhibits both HMT and its therapeutically described target, the acetylcholinesterase.[17] As a common structural feature these and many other HMT inhibitors possess an aminoquinoline or tetrahydroacridine moiety.[25] Therefore, we additionally describe imidazole compounds which were coupled via

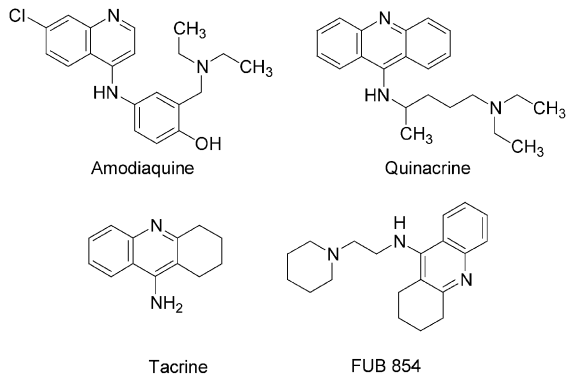


Chart 1. Amodiaquine, quinacrine, and tacrine, inhibitors of HMT, and FUB 854, a prototype HMT inhibitor with combined histamine H_3 receptor antagonist potency.

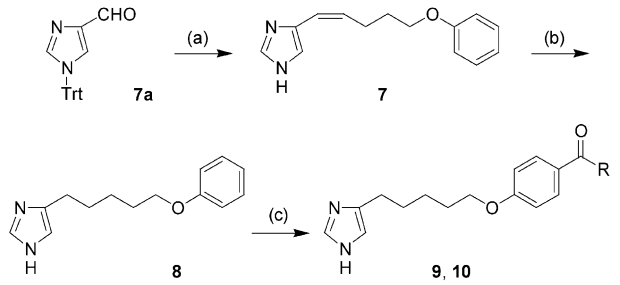
spacers with these special partial structures. For all new compounds, binding affinities at human H_3 receptors stably expressed in CHO cells or antagonist potencies in a functional in vitro assay on synaptosomes of rat cerebral cortex as well as inhibitory activities at rat kidney HMT were determined.

Results and Discussion

Chemistry

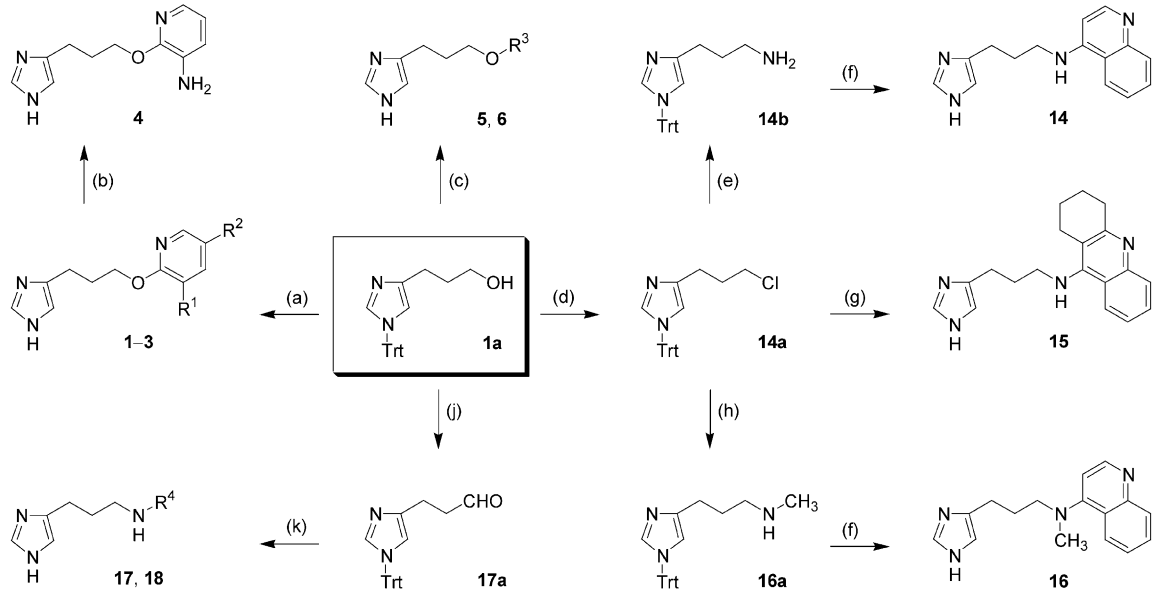
The 2-pyridyl ether derivatives **1–3** were synthesized via aromatic nucleophilic substitution starting from commercially available chloropyridine derivatives and trityl-protected 3-(1*H*-imidazol-4-yl)propanol (**1a**) and subsequent acidic hydrolysis of the protecting group (Scheme 1).[26] Primary aromatic amine derivative **4** was prepared in good yield by catalytic reduction of the nitro group of **2** with hydrogen. The final compounds **5** and **6** were synthesized by phenol etherification of **1a** under Mitsunobu conditions and subsequent hydrolytic cleavage of the protecting group as described above.[27] In the synthesis of **5** the desired phenol reactant was prepared according to Yoshino et al.[28]

In a Wittig reaction, olefin **7** was formed from trityl-protected 1*H*-imidazol-4-ylcarbaldehyde (**7a**) and the phosphonium salt of 4-phenoxybutyl bromide and triphenylphosphine (Scheme 2). The aldehyde **7a** was obtained through modification of a procedure described by Kelley et al.,[29] which started from formamidine and included cyclization to 1*H*-imidazol-4-ylmethanol, subsequent introduction of the trityl group and oxidation



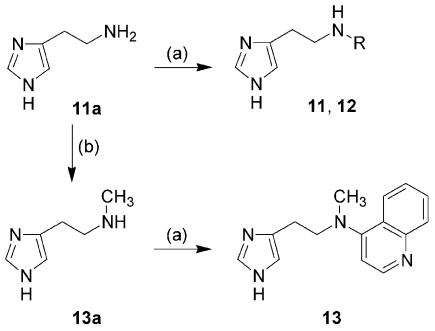
Scheme 2. Synthesis of 5-(1*H*-imidazol-4-yl)pent(en)yl derivatives **7–10**. (a) (i): $PhO(CH_2)_4PPh_3^+Br$, $KOC(CH_3)_3$, THF, 18 h; (ii) 2 N HCl, acetone, reflux, 1 h; (b) H_2 (10 bar), Pd/C, MeOH/2 N HCl, rt, 18 h; (c) corresponding acyl halide, $AlCl_3$, nitrobenzene, rt, 3 days; R = CH_3 (**9**); R = C_2H_5 (**10**).

by manganese(IV)-oxide (not shown). Determination of the *E*:*Z* ratio of the product (based on NMR) showed that the overall sequence as expected gave solely the *Z*-configured olefin. This can be attributed to the ylide formation from a triarylphosphine, the absence of ylide stabilizing groups, and the solvent used (THF). Reduction of **7** with hydrogen and palladium catalysis resulted in the saturated imidazole derivative **8**. The aryl ketones **9** and **10** were prepared from **8** in a Friedel–Crafts acylation with the corresponding acyl halides as reactants and the Lewis acid aluminum chloride as catalyst. Due to the *ortho*/*para*-directing phenyl substituent, the relatively large size of the acyl group, the solvent used (nitrobenzene), the high reaction temperature, and the crystallization conditions the acylation resulted exclusively in the *para*-products. The hydrochloride of **8** was used to avoid possible reaction with the imidazole moiety.



Scheme 1. Synthesis of 3-(1*H*-imidazol-4-yl)propyl derivatives **1–6** and **14–18**. (a) (i) Corresponding chloropyridine, NaH, THF, 60 °C, 12 h; (ii) 2 N HCl, acetone, reflux, 2 h; (b) **2** only: H_2 (1 bar), Pd/C, rt, 18 h; (c) (i) corresponding phenol, Ph_3P, DEAD, THF, rt, 72 h; (ii) 2 N HCl, acetone, reflux, 1 h; (d) $SOCl_2$, THF, rt, 2 h; (e) NH_3 (fl.), $[H_3C(CH_2)_3]_4NI$, NH_4Cl, EtOH, rt, 12 h→60 °C, 24 h; (f) (i) 4-chloroquinoline, phenol, 140 °C, 12 h; (ii) 2 N HCl, THF, reflux, 2 h; (g) (i) 1,2,3,4-tetrahydroacridin-9-amine, NaH, $[H_3C(CH_2)_3]_4NI$, DMF, 140 °C, 12 h; (ii) 2 N HCl, THF, reflux, 2 h; (h) H_3CNH_2, KOH, KI, EtOH/H_2O, reflux, 12 h; (j) $(COCl)_2$, DMSO, $(H_5C_2)_3N$, CH_2Cl_2, −55 °C→rt, 4 h; (k) (i) corresponding aminoquinoline, $Na(CH_3CO_2)_3BH$, H_3CCOOH, 1,2-dichloroethane, rt 3 days; (ii) 2 N HCl, acetone, reflux, 1 h; R^1, R^2 = H (**1**); R^1 = NO_2, R^2 = H (**2**); R^1 = H, R^2 = NO_2 (**3**); R^3 = 4-(3-nitropyridin-2-yl)aminophenoxy (**5**); R^3 = 5-nitroquinolin-8-yloxy (**6**); R^4 = 2-methylquinolin-4-yl (**17**); R^4 = quinolin-6-yl (**18**); Trt = triphenylmethyl.

The synthesis of the 2-(1*H*-imidazol-4-yl)ethyl derivatives **11**–**13** started from histamine (**11a**) which reacted with 4-chloroquinoline or 9-chloro-1,2,3,4-tetrahydroacridine to form target compounds **11** and **12** (Scheme 3). To improve yields the reaction was carried out in molten phenol, in which the formation of unstable phenol ether intermediates with the heterocycles causes increased reactivities as leaving groups compared to those of aryl halides.[30] Adapting the protocol of Mechoulam and Hirshfeld,[31] histamine (**11a**) was cyclized with *N*,*N*′-carbonyldiimidazole and subsequently reduced with $LiAlH_4$. As described above, the resulting N^{α}-monomethylated derivative **13a**[32] was then converted into **13** with 4-chloroquinoline.



Scheme 3. Synthesis of 2-(1*H*-imidazol-4-yl)ethyl derivatives **11**–**13**. (a) Corresponding aryl chloride, phenol, 140 °C, 12 h; (b) (i) *N*,*N*′-carbonyldiimidazole, 100 °C→120 °C, 1 h; (ii) $LiAlH_4$, THF, reflux, 2 h; R = quinolin-4-yl (**11**); R = 1,2,3,4-tetrahydroquinolin-9-yl (**12**).

The key intermediate for the synthesis of 3-(1*H*-imidazol-4-yl)propyl derivatives **14**–**16** was alkyl chloride **14a** which was synthesized from **1a** by reaction with thionyl chloride (Scheme 1).[33] Treatment of **14a** with liquid ammonia at higher pressure and temperature resulted in trityl-protected homohistamine **14b** which was then converted into **14** by N^{α}-alkylation in molten phenol followed by acidic deprotection. Target compound **15** was obtained from **14a** and 1,2,3,4-tetrahydroacridin-9-amine under basic conditions (NaH) and then followed by hydrolysis of the trityl group. The intermediate in the synthesis of **16** N^{τ}-tritylated and N^{α}-methylated histamine (**16a**) was synthesized from **14a**, which was aminated with methyl amine in ethanolic potassium hydroxide. Conversion into **16** was performed under the conditions described in the synthesis of **14**. Target compounds **16** and **17** were prepared by reductive amination of trityl-protected 3-(1*H*-imidazol-4-yl)propanal (**17a**)[34] in the presence of the mild and selective reagent sodium triacetoxyborohydride under acidic conditions. To ensure a fast reaction and to avoid a potential dialkylation, 1,2-dichloroethane was used as solvent and acetic acid was present as acidic catalyst. Aldehyde **17a** was prepared from **1a** by Swern oxidation with oxalyl chloride and dimethyl sulfoxide according to Stark et al.[35] In the final step, the trityl group was cleaved by treatment with hydrochloric acid.

Biological Results and Discussion

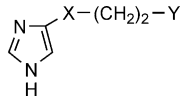
In vitro screening for HMT inhibitory activity

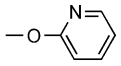
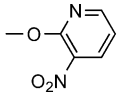
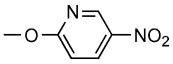
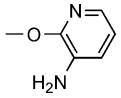
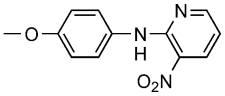
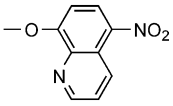
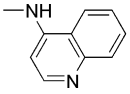
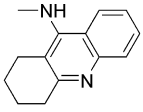
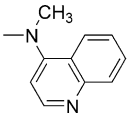
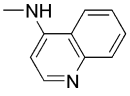
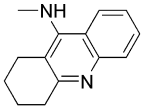
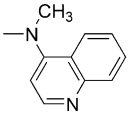
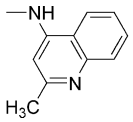
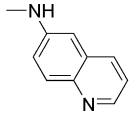
The new compounds were investigated for inhibition of rat kidney HMT activity, using a new technique which was based on the quantitative determination of the metabolite N^{τ}-methylhistamine. The pharmacological data were compared to that of the reference HMT inhibitor tacrine.[17] All compounds described here are inhibitors of rat kidney HMT, which clearly surmount the inhibitory potency of tacrine (Table 1). The imidazole derivatives **1**–**6** which contain (nitro)pyridine or nitroquinoline partial structures exhibited only relatively weak inhibitory potencies. Likewise, the phenyl ether derivatives **7**–**10** inhibit HMT with only moderate potencies. Here, an additional *para*-substituent at the phenyl ring seems to be beneficial. With inhibitory potencies in the low micromolar concentration range (compounds **9** and **10**) the development of the phenyl ether class proved to be a slight advance. However, major improvement in enzyme inhibitory potency was obtained with the next seven compounds, the aminoquinoline- or aminotetrahydroacridine-containing derivatives **11**–**17**. These compounds contain special partial structures that are also integral parts of the standard HMT inhibitors amodiaquine, quinacrine, tacrine, and the novel hybrid compound FUB 854 (cf. Chart 1). Within the homogeneous series described here, the heterocyclic compounds differ from each other in the number of chain methylene groups (two or three) and in the substitution at the aminoquinoline moiety. Moreover, the influence upon introducing an additional alkyl group at the aromatic amino group (**13** and **16**) or quinoline moiety (**12**, **15**, **17**) as well as variation of the substitution pattern from 4- to 6-position (**18**) were investigated. Whereas the potency of the 6-aminoquinoline derivative **18** was in the micromolar concentration range only, all other compounds of this series inhibited the HMT with nanomolar potency. In the compounds with a two carbon linker and also in the derivatives with a trimethylene chain, replacement of the quinoline group by a tetrahydroacridine moiety was well tolerated (**11** vs **12** and **14** vs **15**) and resulted in almost equipotent compounds. Likewise, variation of the distance between the different heterocyclic areas from two to three methylene groups proved to be of some importance since the potencies of all derivatives could be slightly increased (**11** vs **14**, **12** vs **15**, and **13** vs **16**). While a methyl substituent directly attached at the quinoline 2-position led to a decrease in HMT inhibitory potency (**17** vs **14**), the introduction of the additional methyl group at the aromatic amino *N* atom was well tolerated (**13** vs **11** and **16** vs **14**). Since the best compounds reach the extraordinary combined potencies of FUB 854, the imidazole-containing compounds may serve as novel leads if their pharmacokinetic properties are satisfactory. Further investigations are needed in this direction since the standard in vivo assay is based on the formation of N^{τ}-methylhistamine and is therefore not applicable to the novel hybrid compounds.

Histamine H_3 receptor antagonist potency on synaptosomes of rat cerebral cortex

Initially, the novel heterocyclic compounds were additionally evaluated for their abilities to affect the release

Table 1. Chemical structures and pharmacological screening results of novel imidazole derivatives for rat HMT inhibition and rat and human histamine H_3 receptors



No.	X	Y	HMT-Inhibition IC_{50} (μM)[a]	H_3 K_i (nM)
1	$-CH_2-$		76±2	139[b]
2	$-CH_2-$		59±15	117[b]
3	$-CH_2-$		12.7±0.9	5.3[b]
4	$-CH_2-$		40±7	266[b]
5	$-CH_2-$		8.4±0.3	≥530[b]
6	$-CH_2-$		11.7±0.7	48[b]
7	$-CH{=}CH-CH_2-$	$-O-C_6H_5$	28	>30[c]
8	$-(CH_2)_3-$	$-O-C_6H_5$	18.6	0.74[c]
9	$-(CH_2)_3-$	$-O-C_6H_5-4-CO-CH_3$	7.8±2	45[c]
10	$-(CH_2)_3-$	$-O-C_6H_5-4-CO-C_2H_5$	3.6±0.5	86[c]
11	—		0.055±0.002	20[c]
12	—		0.086±0.016	21[c]
13	—		0.079±0.006	47[c]
14	$-CH_2-$		0.024±0.004	4.1[c]
15	$-CH_2-$		0.035±0.004	93[c]
16	$-CH_2-$		0.035±0.004	17[c]
17	$-CH_2-$		0.54±0.06	51[c]
18	$-CH_2-$		6.1±0.2	71[c]
Ciproxifan			9.0±0.2	46[c,d]
FUB 854[e]			0.034±0.001	19[c]
Tacrine[e]			0.11±0.04	n.d.[f]

[a]HMT assay on isolated enzyme from rat kidney [mean value with standard error of the mean (SEM).][21]
[b]Functional H_3 receptor in vitro assay on synaptosomes of rat cerebral cortex.[37]
[c][^{125}I]Iodoproxyfan binding assay at human H_3 receptors stably expressed in CHO cells.[43]
[d]Data from ref 36.
[e]Data from ref 21.
[f]n.d., Not determined.

of [^{3}H]histamine on synaptosomes of rat cerebral cortex (Table 1), a functional assay for in vitro determination of histamine H_3 receptor potency.[37] The compounds investigated in this assay (**1**–**6**) exhibited antagonist properties at histamine H_3 receptors with potencies in the low to high nanomolar concentration range (K_i = 5.3 →530 nM). While the mono-substituted pyridine derivative **1** and the pyridine derivatives with an additional substituent in 3-position (**2**, **4**, **5**) were weak antagonists, antagonist potency could be increased by the aminoquinoline **6** or more pronounced by the 5-nitropyridine derivative **3**.

Binding affinity at cloned human histamine H_3 receptors

The data obtained from the screening at rat HMT showed that compounds **7**–**10** and especially **11**–**18** possess improved inhibitory activities (see above). Therefore to further elaborate structure–activity relationship, we updated and changed our type of the pharmacological investigation to an even more relevant target and determined the affinity of these novel compounds (**7**–**18**) at cloned human histamine H_3 receptors by a [^{125}I]iodoproxyfan binding assay in CHO cells.[21] Except for the alkenyl derivative **7** all compounds investigated proved to be ligands with nanomolar affinity for human histamine H_3 receptors despite their large differences in chain length and (hetero)aromatic substitution. In this series of compounds, the most potent were the aminoquinoline derivative **14** with a three carbon linker between the imidazole and the other heterocyclic moiety and the ether derivative **8** with a five carbon linker. However, compound **8** is a weak HMT inhibitor whereas compound **14** is highly efficient as HMT inhibitor.

Molecular modeling

Preliminary data from molecular modeling investigations showed that the imidazole derivative **15** and the HMT inhibitor quinacrine possess the same binding area (Fig. 1). Molecular docking studies were carried out on the basis of a homology model of rat HMT as described in the methods section. In a first step the refined model was used for docking of the cocrystallized inhibitor quinacrine. The RMSD value (all heavy atoms) between experimentally observed and calculated position is 0.81 Å, indicating the good agreement between docking and X-ray analysis. Further investigation shows that the nonimidazole compound FUB 854,[21] the imidazole **15** and quinacrine are interacting in a similar way with the protein (Fig. 1).

The tetrahydroacridine ring of the analyzed compounds is sandwiched between Tyr147 and Cys196 on the one side and Tyr115 on the other (Fig. 2). The protonated imidazole of compound **15** as well as the protonated piperidine ring of FUB 854 are interacting with the buried acidic binding pocket. A detailed picture of the interaction potential at the binding site is given by GRID calculations[38] using a variety of different probes. Since the binding pocket shows a large favorable interaction region for a cationic head group (results not shown), compounds with varying spacer length between the protonated moiety and the aromatic system are able to interact in a similar way with the aromatic residues at the lower part of the binding pocket (Fig. 2). A manuscript dealing with docking and quantitative structure–activity relationship studies of HMT inhibitors is in preparation.

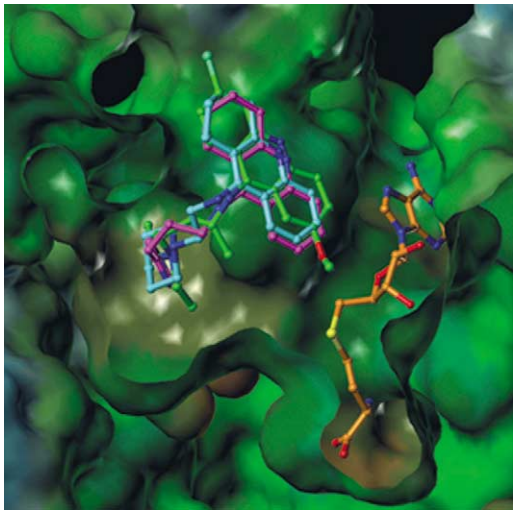


Figure 1. HMT inhibitor interactions: Comparison between the experimentally observed structure of quinacrine (green) and the docked compounds imidazole **15** (magenta) and FUB 854 (cyan). The co-crystallized reaction product *S*-adenosylhomocysteine is colored orange. The protein surface is colored according to the hydrophobic potential (blue = hydrophilic areas, brown = hydrophobic areas, calculated with the MOLCAD software).[45]

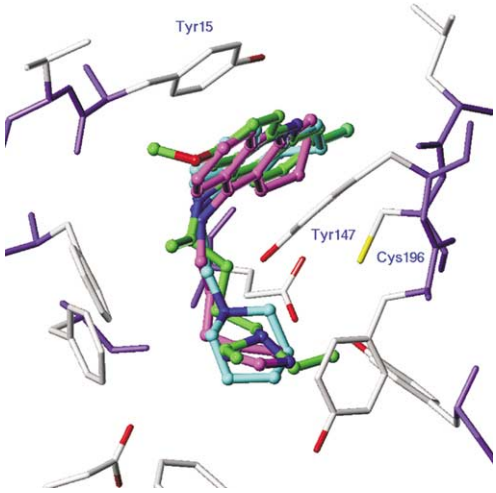


Figure 2. HMT inhibitor interactions: The acridine and tetrahydroacridine ring system, respectively, is sandwiched between Tyr147 and Cys196 on the one side and Tyr15 on the other. The cationic head of the compounds is interacting with several aromatic residues located at the bottom of the binding pocket.

Conclusion

Starting from several aromatic carbo- or heterocyclic partial structures (e.g., aminoquinoline or tetrahydroacridine moieties) of standard HMT inhibitors a new class of drugs has been designed in which these moieties are linked by different alkyl and alkenyl spacers to an additional imidazole heterocycle which is also an integral part of potent H_3 receptor antagonists. Combination of these structural features could pharmacologically implement a dual mode of action: Histamine H_3 receptor affinity and inhibitory potencies at rat kidney HMT. Depending on the nature of the aromatic system derived from the reference HMT inhibitors some compounds displayed remarkable affinities for H_3 receptors, but only moderate potencies at rat HMT. However, with the interesting aminoquinoline or 1,2,3,4-tetrahydroacridine derivatives the HMT inhibitory potency was strongly increased. In this series, the quinoline-containing compound **14** in particular combines high H_3 receptor affinity with high HMT inhibitory activity. These novel compounds represent a new class of hybrid drugs which are useful pharmacological tools for the evaluation of (patho)physiological functions of brain histamine and potential drugs in numerous CNS disorders, for example, neurodegenerative diseases or schizophrenia.

Experimental

Chemistry

General procedures. Melting points (mp) were determined on an Electrothermal IA 9000 digital or a Büchi 512 apparatus. ^{1}H NMR spectra were recorded on a Bruker DPX 400 Avance spectrometer (400 MHz) in dimethylsulfoxide-d_6 as standard solvent, unless stated otherwise. Chemical shifts are reported in ppm downfield from internal tetramethylsilane as a reference. ^{1}H NMR signals are reported in order: multiplicity (s,

singlet; d, doublet; dd, doublet of a doublet; t, triplet; q, quartet; m, multiplet; *, exchangeable by D_2O), approximate coupling constants in Hertz, and number of protons. EI mass spectra were obtained on a Finnigan MAT CH7A (70 eV, 170 °C) and FAB^+ spectra were recorded on a Finnigan MAT CH5DF (Xe, 80 eV, Me_2SO as solvent, glycerol as matrix). Elemental analyses (C, H, N) were measured for final compounds on Perkin-Elmer 240 B or Perkin-Elmer 240 C instruments and are within ±0.4% of the theoretical values (Table 2). All final compounds were crystallized and recrystallized as salts of oxalic acid or hydrochloric acid from ethanol/diethyl ether unless otherwise indicated. Column chromatography was carried out using silica gel 63–200 µm (Merck) and flash chromatography was performed with silica gel 40–63 µm (Merck). Thin layer chromatography was performed on silica gel F_{254} plates (Merck). The following abbreviations are used: Acr, 1,2,3,4-tetrahydroacridin-9-yl; CF_3COOD, trifluoroacetic acid-d_4; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; Et_2O, diethyl ether; EtOAc, ethyl acetate; EtOH, ethanol; Im, 1*H*-imidazol-4-yl; MeOH, methanol; Ph, phenyl; Quin, quinolinyl; rt, room temperature; THF, tetrahydrofuran.

General procedure for the preparation of imidazole derivatives 1–3

A suspension of 3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanol (**1a**, 0.92 g, 2.5 mmol)[26] and NaH (suspended in mineral oil, ω = 60%, 0.07 g, 3 mmol) in dry THF (30 mL) was stirred for 1 h at 60 °C. After cooling to rt the corresponding 2-chloropyridine derivative (2.5 mmol) was added and the mixture was refluxed for 12 h. After removal of the solvent under reduced pressure, the residue was dissolved in EtOAc and washed with a solution of K_2CO_3 in H_2O. The organic layer was concentrated in vacuo and the residue was purified by column chromatography (eluent: EtOAc). The resulting crude product was dissolved in acetone (15 mL), aqueous HCl (c = 2 mol/l, 15 mL) was added and the mixture was heated under reflux for 2 h. After removal of the organic solvent, filtration, and extraction with Et_2O the aqueous phase was basified (K_2CO_3) and extracted with CH_2Cl_2. The latter organic extracts were combined, washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure.

3-(1*H*-Imidazol-4-yl)propyl pyridin-2-yl ether hydrogen oxalate (1). From 2-chloropyridine. Yield: 25%; ^{1}H NMR δ 2.04 (m, 2H, ImCH$_2$CH_2), 2.72 (t, J = 7.5 Hz, 2H, ImCH_2), 4.26 (t, J = 6.4 Hz, 2H, OCH_2), 6.78 (d, J = 8.4 Hz, 1H, Pyr-3*H*), 6.95 (m, 1H, Pyr-5*H*), 7.16 (s, 1H, Im-5*H*), 7.69 (m, 1H, Pyr-4*H*), 8.13 (d, J = 4.9 Hz, 1H, Py-6*H*), 8.34 (s, 1H, Im-2*H*); EI–MS m/z (%) 203 ($M^{+\bullet}$, 6).

3-(1*H*-Imidazol-4-yl)propyl 3-nitropyridin-2-yl ether hydrochloride (2). From 2-chloro-3-nitropyridine. Yield: 50%; ^{1}H NMR δ 2.13 (m, 2H, ImCH$_2$CH_2), 2.83 (t, J = 7.5 Hz, 2H, ImCH_2), 4.49 (t, J = 6.2 Hz, 2H, OCH_2), 7.23–7.26 (m, 1H, Pyr-5*H*), 7.45 (s, 1H, Im-5*H*), 8.42–8.50 (m, 2H, Pyr-4,6*H*), 8.98 (s, 1H, Im-2*H*); EI–MS m/z (%) 248 ($M^{+\bullet}$, 10).

3-(1*H*-Imidazol-4-yl)propyl 5-nitropyridin-5-yl ether hydrogen oxalate (3). From 2-chloro-5-nitropyridine. Yield: 27%; ^{1}H NMR δ 2.09 (m, 2H, ImCH$_2$CH_2), 2.76 (t, J = 7.4 Hz, 2H, ImCH_2), 4.42 (t, J = 6.3 Hz, 2H, OCH_2), 7.01 (m, 1H, Pyr-3*H*), 7.24 (s, 1H, Im-5*H*), 8.48 (m, 2H, Pyr-4,6*H*), 9.06 (s, 1H, Im-2*H*); EI–MS m/z (%) 248 ($M^{+\bullet}$, 6).

2-[3-(1*H*-Imidazol-4-yl)propoxy]pyridin-3-amine hydrogen oxalate (4). A mixture of **2** (free base, 0.16 g, 0.65 mmol) and palladium (on carbon, ω = 10%, 0.03 g) in dry THF (20 mL) was stirred under hydrogen (p = 1 bar) for 18 h at rt. Filtration and removal of the solvent under reduced pressure resulted in a colourless oil. Yield: 92%; ^{1}H NMR δ 2.06 (m, 2H, ImCH$_2$CH_2),

Table 2. Physical properties and elemental analysis of imidazole derivatives 1–18

No.	Formula	M_w[a] (g/mol)	Mp (°C)	Calculated (%)			Found (%)		
				C	H	N	C	H	N
1	$C_{11}H_{13}N_3O{\cdot}C_2H_2O_4$	319.3	114	56.4	5.37	13.2	56.3	5.36	13.0
2	$C_{11}H_{12}N_4O_3{\cdot}HCl{\cdot}0.25H_2O$	289.0	173	45.7	4.53	19.4	45.9	4.61	19.2
3	$C_{11}H_{12}N_4O_3{\cdot}C_2H_2O_4$	338.3	209	46.2	4.17	16.6	46.0	4.20	16.4
4	$C_{11}H_{14}N_4O{\cdot}C_2H_2O_4{\cdot}0.5H_2O$	317.3	145	49.6	5.24	17.4	49.6	5.25	17.4
5	$C_{17}H_{17}N_5O_3{\cdot}C_2H_2O_4$	429.4	225	53.2	4.46	16.3	52.9	4.38	16.15
6	$C_{15}H_{14}N_4O_3{\cdot}C_2H_2O_4{\cdot}0.75H_2O$	401.9	209	50.8	4.01	13.9	50.9	4.14	13.8
7	$C_{14}H_{16}N_2O{\cdot}C_2H_2O_4{\cdot}0.5H_2O$	326.3	195	58.7	5.69	8.55	58.9	5.63	8.55
8	$C_{14}H_{18}N_2O{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	324.9	174	59.2	6.36	8.62	59.0	6.12	8.74
9	$C_{16}H_{20}N_2O_2{\cdot}C_2H_2O_4$	362.4	183	59.7	6.12	7.73	59.8	6.17	7.36
10	$C_{17}H_{22}N_2O_2{\cdot}C_2H_2O_4$	376.4	190	60.6	6.43	7.44	60.8	6.28	7.70
11	$C_{14}H_{14}N_4{\cdot}2.7HCl$	336.7	238–239	49.8	5.00	16.6	50.0	5.25	16.3
12	$C_{15}H_{16}N_4{\cdot}1.5C_2H_2O_4{\cdot}H_2O$	405.4	151	53.3	5.22	13.8	53.3	5.22	13.6
13	$C_{18}H_{20}N_4{\cdot}2C_2H_2O_4$	472.5	204	55.9	5.12	11.9	55.6	5.01	11.72
14	$C_{15}H_{16}N_4{\cdot}2.6C_2H_2O_4$	486.4	189	49.9	4.39	11.5	49.8	4.51	11.5
15	$C_{16}H_{18}N_4{\cdot}2C_2H_2O_4{\cdot}H_2O$	464.4	84	51.7	5.21	12.1	51.7	5.24	12.1
16	$C_{19}H_{22}N_4{\cdot}2C_2H_2O_4{\cdot}1.25H_2O$	509.0	152	54.3	5.64	11.0	54.3	5.55	10.7
17	$C_{16}H_{18}N_4{\cdot}2C_2H_2O_4{\cdot}1.5H_2O$	473.4	203	50.7	5.32	11.8	50.9	5.13	11.4
18	$C_{15}H_{16}N_4{\cdot}2C_2H_2O_4$	432.4	205	52.8	4.66	13.0	52.8	4.68	12.8

[a] M_w, molecular weight.

2.79 (t, $J=7.5$ Hz, 2H, ImCH_2), 4.25 (t, $J=6.2$ Hz, 2H, OCH_2), 6.68 (dd, $J_{4H/5H}=7.5$ Hz, $J_{5H/6H}=4.9$ Hz, 1H, Pyr-5*H*), 6.86 (d, $J=7.5$ Hz, 1H, Pyr-4*H*), 7.26 (s, 1H, Im-5*H*), 7.31 (d, $J=4.8$ Hz, 1H, Py-6*H*), 8.58 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 218 ($M^{+\bullet}$, 3).

General procedure for the preparation of imidazole derivatives 5 and 6

3-[1-(Triphenylmethyl)-1*H*-imidazol-4-yl]propanol (**1a**, 0.92 g, 2.5 mmol),[26] triphenylphosphine (0.65 g, 2.5 mmol), and the corresponding phenol (2.5 mmol) were dissolved in freshly distilled THF (15 mL) under argon atmosphere and ice-cooling. Then, diethyl azodicarboxylate (0.7 g, 3 mmol) was slowly added followed by additional stirring for 72 h at rt After removal of the solvent in vacuo the crude product was purified by column chromatography (eluent: EtOAc). The oily residue was dissolved in acetone (20 mL), aqueous HCl ($c=2$ mol/L, 20 mL) was added and the mixture was refluxed for 1 h. After removal of the organic solvent, filtration, and extraction with Et_2O the aqueous phase was basified (K_2CO_3) and extracted with CH_2Cl_2. The latter organic extracts were combined, washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure.

***N*-(3-Nitropyridin-2-yl)-4-[3-(1*H*-imidazol-4-yl)propoxy]-aniline hydrogen oxalate (5).** From 4-[(3-nitropyridin-2-yl)amino]phenol.[28] Yield: 30%; ^{1}H NMR δ 2.06 (m, 2H, ImCH$_2$CH_2), 2.78 (t, $J=7.3$ Hz, 2H, ImCH_2), 4.01 (t, $J=6.0$ Hz, 2H, OCH_2), 6.93 (m, 3H, Ph-3,5*H*, Pyr-5*H*), 7.26 (s, 1H, Im-5*H*), 7.49 (d, $J=8.7$ Hz, 2H, Ph-2,6*H*), 8.46 (s, 1H, Im-2*H*), 8.51 (m, 2H, Py-4,6*H*), 9.87 (s*, 1H, NH); EI–MS *m*/*z* (%) 339 ($M^{+\bullet}$, 3).

3-(1*H*-Imidazol-4-yl)propyl 5-nitroquinolin-8-yl ether hydrogen oxalate (6). From 5-nitroquinolin-8-ol. Yield: 50%; ^{1}H NMR δ 2.25 (m, 2H, ImCH$_2$CH_2), 2.89 (t, $J=7.2$ Hz, 2H, ImCH_2), 4.39 (t, $J=6.1$ Hz, 2H, OCH_2), 7.29 (s, 1H, Im-5*H*), 7.35–7.38 (d, $J=8.9$ Hz, m, 1H, Quin-7*H*), 7.85–7.89 (m, 1H, Quin-3*H*), 8.55 (s, 1H, Im-2*H*), 8.57 (d, $J=8.9$ Hz, 1H, Quin-6*H*), 9.05–9.07 (m, 2H, Quin-2,4*H*); EI–MS *m*/*z* (%) 298 ($M^{+\bullet}$, 2).

(*Z*)-5-(1*H*-Imidazol-4-yl)pent-4-enyl phenyl ether hydrogen oxalate (7). A solution of triphenylphosphine (8.14 g, 35 mmol) and 4-(phenoxy)butyl bromide (9.32 g, 35 mmol) in toluene (100 mL) was refluxed for 3 days. After cooling the precipitated product was isolated, washed successively with toluene and petroleum ether, and added to a solution of (1-triphenylmethyl-1*H*-imidazol-4-yl)carbaldehyde (**7a**, 13.15 g, 38.9 mmol)[29] in freshly distilled THF (200 mL). Potassium *tert*-butanolate (4.7 g, 42 mmol) was added and the mixture was stirred at rt for 18 h under argon. The solvent was removed in vacuo, the residue dissolved in H_2O and extracted with $CHCl_3$. The organic extracts were combined, washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure. The oily residue was dissolved in acetone (15 mL), aqueous HCl ($c=2$ mol/L, 15 mL) was added and the mixture was refluxed for 1 h. After removal of the organic solvent, filtration, and extraction with Et_2O the aqueous phase was basified (K_2CO_3) and extracted with CH_2Cl_2. The latter organic extracts were combined, washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure. Yield: 44%; ^{1}H NMR δ 2.01 (m, 2H, OCH$_2$CH_2), 2.60 (m, 2H, CH=CHCH_2), 4.05 (t, $J=6.1$ Hz, 2H, OCH_2), 5.61 (q, $J_{CH=CH/CH2}=11.6$ Hz, $J_{CH2/CH2}=7.5$ Hz, 1H, ImCH=C*H*), 6.35 (d, $J=11.6$ Hz, 1H, ImC*H*=CH), 6.91–6.93 (m, 3H, OPh-3,4,5*H*), 7.08 (s, 1H, Im-5*H*), 7.29 (m, 2H, OPh-2,6*H*), 7.58 (s, 1H, Im-2*H*); FAB$^+$-MS *m*/*z* (%) 229 ($M+H^+$, 100).

5-(1*H*-Imidazol-4-yl)pentyl phenyl ether hydrogen oxalate (8). A mixture of **7** (free base, 0.3 g, 1.31 mmol), MeOH (10 mL), aqueous HCl ($c=2$ mol/L, 10 mL) and palladium (on carbon, ω = 10%, 0.04 g) was stirred under hydrogen ($p=10$ bar) for 18 h at rt After filtration and removal of the solvent under reduced pressure the residue was dissolved in a solution of potassium carbonate in H_2O and extracted with CH_2Cl_2. The organic extracts were combined, washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure. Yield: 40%; ^{1}H NMR δ 1.44 (m, 2H, ImCH$_2$CH$_2$CH_2), 1.65–1.75 (m, 4H, ImCH$_2$CH_2, PhOCH$_2$CH_2), 2.63 (t, $J=7.4$ Hz, 2H, ImCH_2), 3.95 (t, $J=6.4$ Hz, 2H, PhOCH_2), 6.91–6.93 (m, 3H, OPh-3,4,5*H*), 7.22–7.29 (m, 3H, Im-5*H*, OPh-2,6*H*), 8.55 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 229 ($M^{+\bullet}$, 17).

General procedure for the preparation of imidazole derivatives 9 and 10

Aluminum chloride (2.8 g, 21 mmol) was slowly added to a solution of the corresponding acyl halide (7 mmol) in nitrobenzene (10 mL) under ice-cooling. Then, **8**•HCl (0.66 g, 2.5 mmol) was added, and the mixture was stirred for 3 days at rt The mixture was then diluted with toluene (50 mL) and extracted with aqueous HCl ($c=5$ mol/L). The aqueous layer was basified and extracted with CH_2Cl_2. The organic extracts were combined and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (eluent: CH_2Cl_2/MeOH; 95:5).

4-[5-(1*H*-Imidazol-4-yl)pentoxy]acetophenone hydrogen oxalate (9). From acetyl chloride. Yield: 30%; ^{1}H NMR (CF_3COOD) δ 1.69 (m, 2H, ImCH$_2$CH$_2$CH_2), 1.89 (m, 2H, ImCH$_2$CH_2), 1.98 (m, 2H, OCH$_2$CH_2), 2.77 (s, 3H, CH_3), 2.89 (t, $J=7.7$ Hz, 2H, ImCH_2), 4.25 (t, $J=6.3$ Hz, 2H, OCH_2), 7.08 (d, $J=8.9$ Hz, 2H, Ph-3,5*H*), 7.23 (s, 1H, Im-5*H*), 8.11 (d, $J=8.9$ Hz, 2H, Ph-2,6*H*), 8.57 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 272 ($M^{+\bullet}$, 4).

1-{4-[5-(1*H*-Imidazol-4-yl)pentoxy]}propiophenone hydrogen oxalate (10). From propionyl chloride. Yield: 70%; ^{1}H NMR (CF_3COOD) δ 1.34 (t, $J=7.4$ Hz, 3H, CH_3); 1.69 (m, 2H, ImCH$_2$CH$_2$CH_2), 1.89 (m, 2H, ImCH$_2$CH_2), 1.98 (m, 2H, OCH$_2$CH_2), 2.88 (q, $J=7.4$ Hz, 2H, CH_2CH$_3$), 3.15 (t, $J=7.5$ Hz, 2H, ImCH_2), 4.25 (t, $J=6.3$ Hz, 2H, OCH_2), 7.08 (d, $J=8.8$ Hz, 2H, Ph-3,5*H*), 7.23 (s, 1H, Im-5*H*), 8.09 (d, $J=8.8$ Hz, 2H, Ph-2,6*H*), 8.56 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 286 ($M^{+\bullet}$, 5).

General procedure for the preparation of imidazole derivatives 11–13

Histamine (**11a**, 0.33 g, 3 mmol) or *N*-methyl-2-(1*H*-imidazol-4-yl)ethanamine (**13a**, 0.35 g, 2.8 mmol),[32] the corresponding aryl chloride (2.5 mmol) and phenol (3 g, 31.9 mmol) were stirred at 140 °C for 12 h. After cooling aqueous NaOH ($c = 6$ mol/L) and EtOAc were added and the mixture was stirred for 1 h at rt The organic layer was separated, washed (aqueous NaOH), and the solvent was removed in vacuo. The residue was purified by column chromatography (eluent: EtOAc/MeOH/triethylamine; 95:5:5).

***N*-Quinolin-4-yl-2-(1*H*-imidazol-4-yl)ethanamine dihydrochloride (11).** From **11a** and 4-chloroquinoline. Yield: 42%; ^{1}H NMR δ 3.10 (t, $J = 6.7$ Hz, 2H, ImCH_2), 3.90 (s, 2H, NCH_2), 7.00 (m, $J = 7.3$ Hz, 1H, Quin-3*H*), 7.57 (s, 1H, Im-4*H*), 7.70–8.00 (m, 3H, Quin-6*H*, Quin-7*H*, Quin-5*H*), 8.56 (t, $J = 7.8$, 1H, Quin-2*H*), 8.64 (m, 1H, Quin-8*H*), 9.07 (s, 1H, Im-2*H*); APCI-MS *m*/*z* (%) 239.2 ([M + H]$^{+\bullet}$, 100).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-2-(1*H*-imidazol-4-yl)ethanamine dihydrogen oxalate (12).** From **11a** and 9-chloro-1,2,3,4-tetrahydroacridine. Yield: 44%; ^{1}H NMR δ 1.84 (m, 4H, 2Acr-2,3*H*), 2.63 (m, 2H, 2Acr-4*H*), 2.97 (m, 2H, 2Acr-1*H*), 3.06 (t, $J = 6.7$ Hz, 2H, ImCH_2), 4.15 (t, $J = 6.3$ Hz, 2H, CH_2NAcr), 7.16 (s, 1H, Im-5*H*), 7.59 (m, 1H, Acr-6*H*), 7.88 (m, 1H, Acr-8*H*), 7.82 (m, 1H, Acr-7*H*), 8.37 (s, 1H, Im-2*H*), 8.54 (d, $J = 8.8$ Hz, 1H, Acr-5*H*); EI–MS *m*/*z* (%) 292 (M$^{+\bullet}$, 18).

***N*-Methyl-*N*-quinolin-4-yl-2-(1*H*-imidazol-4-yl)ethanamine dihydrogen oxalate (13).** From **13a** and 4-chloroquinoline. Yield: 35%; ^{1}H NMR δ 3.48 (t, $J = 7.5$ Hz, 2H, ImCH_2); 3.68 (s, 3H, CH_3), 4.27 (t, $J = 7.4$ Hz, 2H, CH_2NQuin), 7.07 (d, $J = 7.3$ Hz, 1H, Quin-3*H*), 7.45 (s, 1H, Im-5*H*), 7.76 (m, 1H, Quin-6*H*), 7.92 (d, $J = 8.5$ Hz, 1H, Quin-5*H*), 8.01 (m, 1H, Quin-7*H*), 8.32 (d, $J = 7.2$ Hz, 1H, Quin-2*H*), 8.34 (d, $J = 9.2$ Hz, 1H, Quin-8*H*), 8.67 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 252 (M$^{+\bullet}$, 9).

3-(1-Triphenylmethyl-1*H*-imidazol-4-yl)propanamine (14b). In an autoclave 4-(3-chloropropyl)-1-(triphenylmethyl)-1*H*-imidazole hydrochloride (**14a**, 1.01 g, 2.4 mmol),[33] catalytic amounts of tetra-*n*-butylammonium chloride and NH_4Cl, and EtOH (50 mL) were cooled to 0 °C. Liquid ammonia (150 mL) was added and the mixture was stirred for 12 h at rt and then for 24 h at 60 °C (p = 20-25 bar). After cooling, ablation of the ammonia and removal of the solvent under reduced pressure the residue was purified by flash chromatography (eluent: CH_2Cl_2/MeOH, NH_3-satd.; 95:5). Yield: 67%; ^{1}H NMR δ 1.66 (m, 2H, ImCH$_2$CH_2), 2.45 (t, $J = 7.0$ Hz, 2H, CH_2N), 2.60 (t, $J = 7.4$ Hz, 2H, ImCH_2), 6.60 (s, 1H, Im-5*H*), 7.08 (m, 6H, 6Ph), 7.25 (s, 1H, Im-2*H*), 7.39 (m, 9H, 9Ph); EI–MS *m*/*z* (%) 367 (M$^{+\cdot}$, 1).

***N*-Quinolin-4-yl-3-(1*H*-imidazol-4-yl)propanamine dihydrogen oxalate (14).** 4-Chloroquinoline (0.41 g, 2.5 mmol), **14b** (0.94 g, 2.5 mmol) and phenol (3 g, 31.9 mmol) were stirred at 140 °C for 12 h. After cooling aqueous NaOH ($c = 6$ mol/L) and EtOAc were added and the mixture was stirred for 1 h at rt The organic layer was isolated, washed (aqueous NaOH), and the solvent was removed in vacuo. The residue was dissolved in THF (15 mL) and aqueous HCl ($c = 2$ mol/L, 15 mL) was added. After being heated under reflux for 2 h the organic solvent was removed under reduced pressure. The aqueous layer was filtrated, washed (CH_2Cl_2), basified, and extracted with CH_2Cl_2. After removal of the solvent in vacuo the crude product was purified by flash chromatography (eluent: EtOAc/MeOH/triethylamine; 95:10:5). Yield: 55%; ^{1}H NMR (CF_3COOD) δ 2.36 (m, 2H, ImCH$_2$CH_2), 3.07 (t, $J = 7.8$ Hz, 2H, ImCH_2), 3.82 (t, $J = 7.1$ Hz, 2H, CH_2NHQuin), 6.85 (d, $J = 7.1$ Hz, 1H, Quin-3*H*), 7.33 (s, 1H, Im-5*H*), 7.79 (m, 1H, Quin-6*H*), 7.88 (d, $J = 8.5$ Hz, 1H, Quin-5*H*), 8.01 (m, 1H, Quin-7*H*), 8.20 (d, $J = 8.5$ Hz, 1H, Quin-8*H*), 8.32 (d, $J = 7.1$ Hz, 1H, Quin-2*H*), 8.60 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 252 (M$^{+\bullet}$, 22).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-3-(1*H*-imidazol-4-yl)-propanamine dihydrogen oxalate (15).** NaH (suspended in mineral oil, ω = 60%, 0.3 g, 7.5 mmol) was added to a solution of 1,2,3,4-tetrahydroacridin-9-amine (0.99 g, 5 mmol) in dry DMF (20 mL). After stirring for 1 h at 60 °C and subsequent cooling to rt compound **14a** (0.92 g, 2.5 mmol)[33] and a catalytic amount of tetra-*n*-butylammonium iodide were added. The mixture was stirred for 12 h at 140 °C. After removal of the solvent in vacuo and addition of EtOAc and H_2O the organic layer was washed with an aqueous solution of K_2CO_3. The organic solvent was removed under reduced pressure, THF (15 mL) and aqueous HCl ($c = 2$ mol/L, 15 mL) were added, and the mixture was stirred and heated for 2 h under reflux. The organic solvent was removed under reduced pressure and the aqueous layer was filtrated, washed (CH_2Cl_2), basified, and extracted with CH_2Cl_2. The organic extracts were combined and after removal of the solvent in vacuo the crude product was purified by flash chromatography (eluent: EtOAc/MeOH/triethylamine; 95:5:5). Yield: 8%; ^{1}H NMR (CF_3COOD) δ 2.08 (m, 4H, 2Acr-2,3*H*), 2.38 (m, 2H, ImCH$_2$CH_2), 2.72 (m, 2H, 2Acr-1*H*), 3.07 (m, 4H, ImCH_2, 2Acr-4*H*), 4.21 (t, $J = 7.2$ Hz, 2H, CH_2NHAcr), 7.32 (s, 1H, Im-5*H*), 7.65 (m, 1H, Acr-6*H*), 7.77 (d, $J = 8.5$ Hz, 1H, Acr-8*H*), 7.90 (m, 1H, Acr-7*H*), 8.35 (d, $J = 8.7$ Hz, 1H, Acr-5*H*), 8.61 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 306 (M$^{+\bullet}$, 18).

***N*-Methyl-3-(1*H*-imidazol-4-yl)propanamine (16a).** Methanamine (solution in EtOH, ω = 33%, 15 mL, 150 mmol), KOH (2.8 g, 50 mmol), **14a** (0.5 g, 7.5 mmol),[33] and KI (catalytic amount) were dissolved in H_2O (15 mL) and stirred under reflux for 12 h. After removal of the solvent in vacuo and addition of EtOAc and H_2O the organic layer was separated and washed (H_2O). After removal of the solvent in vacuo the crude product was purified by flash chromatography (eluent: EtOAc→CH_2Cl_2/MeOH, NH_3-satd.; 95:5). Yield: 34%; ^{1}H NMR (CF_3COOD) δ 2.34 (m, 2H, ImCH$_2$CH_2), 3.00 (m, 5H, CH_2NHCH_3), 3.38 (m, 2H, ImCH_2), 7.35 (s, 1H,

Im-5*H*), 7.76 (m, 6H, 6Ph*H*), 7.94 (m, 9H, 9Ph*H*), 8.61 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 381 ($M^{+\bullet}$, 1).

***N*-Methyl-*N*-quinolin-4-yl-3-(1*H*-imidazol-4-yl)propanamine dihydrogen oxalate (16).** Synthesis was performed as described for **14** from **16a** (0.95 g, 2.5 mmol). Yield: 23%; ^{1}H NMR (CF_3COOD) δ 2.42 (m, 2H, $ImCH_2CH_2$), 3.00 (t, J = 8.2 Hz, 2H, $ImCH_2$), 3.65 (s, 3H, CH_3), 4.00 (t, J = 7.7 Hz, 2H, CH_2N), 6.98 (d, J = 7.3 Hz, 1H, Quin-3*H*), 7.33 (s, 1H, Im-5*H*), 7.73 (m, 1H, Quin-6*H*), 7.89 (d, J = 8.6 Hz, 1H, Quin-5*H*), 7.98 (m, 1H, Quin-7*H*), 8.26 (d, J = 7.3 Hz, 1H, Quin-2*H*), 8.32 (d, J = 8.6 Hz, 1H, Quin-8*H*), 8.62 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 266 ($M^{+\bullet}$, 41).

General procedure for the preparation of imidazole derivatives 17 and 18

3 - [1 - (Triphenylmethyl) - 1*H* - imidazol - 4 - yl]propanal (0.92 g, 2.5 mmol)[34] and the corresponding aminoquinoline derivative (3 mmol) were dissolved in 1,2-dichloroethane. After addition of glacial acetic acid (0.9 g, 15 mmol) the mixture was stirred at rt for 1 h. Sodium triacetoxyborohydride (2.4 g, 11.3 mmol) was added and the mixture stirred at rt for 3 days. The solvent was removed under reduced pressure, acetone (20 mL) and aqueous HCl (c = 2 mol/L, 20 mL) were added, and the mixture was refluxed for 1 h. The organic solvent was removed under reduced pressure and the aqueous layer was filtrated, washed (Et_2O), basified, and extracted with CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4) and after removal of the solvent in vacuo the crude product was purified by column chromatography (eluents: EtOAc/petroleum ether/triethylamine; 95:150:5 → EtOAc/MeOH/triethylamine; 95:5:5).

***N*-(2-Methylquinolin-4-yl)-3-(1*H*-imidazol-4-yl)propanamine dihydrogen oxalate (17).** From 2-methylquinolin-4-amine. Yield 34%; ^{1}H NMR δ 2.03 (m, 2H, $ImCH_2CH_2$) 2.64 (s, 3H, CH_3), 2.75 (t, J = 7.4 Hz, 2H, $ImCH_2$), 3.54 (t, J = 6.4 Hz, 2H, CH_2N), 6.77 (s, 1H, Quin-3*H*), 7.21 (s, 1H, Im-5*H*), 7.65 (m, 1H, Quin-6*H*), 7.85–7.90 (m, 2H, Quin-5,7*H*), 8.42 (s, 1H, Im-2*H*), 8.48 (d, J = 8.5 Hz, 1H, Quin-8*H*), 9.15 (s*, 1H, NH); EI–MS *m*/*z* (%) 266 ($M^{+\bullet}$, 27).

***N*-Quinolin-6-yl-3-(1*H*-imidazol-4-yl)propanamine dihydrogen oxalate (18).** From quinolin-6-amine. Yield: 43%; ^{1}H NMR δ 1.96 (m, 2H, $ImCH_2CH_2$), 2.78 (t, J = 7.5 Hz, 2H, $ImCH_2$), 3.16 (t, J = 6.7 Hz, 2H, CH_2NH), 6.67 (s, 1H, Quin-5*H*), 7.22 (d, J = 9.1 Hz, 1H, Quin-7*H*), 7.29–7.32 (dd, $J_{2H/3H}$ = 4.0 Hz, $J_{3H/4H}$ = 8.2 Hz, 1H, Quin-3*H*), 7.38 (s, 1H, Im-5*H*), 7.71 (d, J = 9.1 Hz, 1H, Quin-8*H*), 7.99 (d, J = 8.1 Hz, 1H, Quin-4*H*), 8.47 (d, J = 3.8 Hz, 1H, Quin-2*H*), 8.81 (s, 1H, Im-2*H*); EI–MS *m*/*z* (%) 252 ($M^{+\bullet}$, 73).

Pharmacology

Inhibition of histamine *N*-methyltransferase (HMT). All novel compounds were investigated for inhibition of rat kidney activity according to Apelt et al.[21] In brief, HMT was isolated from rat kidneys and purified by a procedure developed by Bowsher et al.[39] with slight modification.[40] Compounds were incubated in different concentrations at 37 °C in a phosphate buffer (c = 20 mmol/L, pH 8.0) together with histamine (c = 1 μmol/L, final concentration) and *S*-adenosyl-L-methionine (c = 20 μmol/L, final concentration) in the presence of HMT. After 20 min, the reaction was stopped by addition of ice-cold perchloric acid (c = 0.4 mol/L, final concentration). The N^{τ}-methylhistamine formed was measured by a specific enzyme-immunoassay. From the curve [concentration of inhibitor]·[N^{τ}-methylhistamine concentration] is calculated the IC_{50} value for each compound. With the exception of **7** and **8** (single experiments) HMT inhibition was investigated at least in triplicate for each compound.

Histamine H_3 receptor antagonist potency in vitro on synaptosomes of rat cerebral cortex. Antagonist potency of the novel compounds **1**–**6** was investigated using an in vitro protocol where K^+-evoked depolarization induces [^{3}H]histamine release from rat synaptosomes.[37] The synaptosomal fraction was prepared according to Whittaker,[41] preincubated with L-[^{3}H]histidine (0.4 μM) at 37 °C for 30 min in a modified Krebs–Ringer solution, washed extensively, and transferred into a fresh Krebs-Ringer buffer containing 2 mM K^+. Compounds alone or together with 1 μM histamine were added 5 min before the depolarization stimulus (30 mM K^+ final concentration). Incubation was terminated by rapid centrifugation. [^{3}H]Histamine levels were determined after ion-exchange chromatography by liquid scintillation spectrometry.[37] K_i values were calculated according to Cheng and Prusoff.[42] Data are presented as mean of experiments performed at least in triplicate.

[^{125}I]Iodoproxyfan binding assay. Potency of the novel compounds **7**–**18** was investigated in a radioligand binding assay described by Ligneau et al.[43] Transfected CHO-K1 cells were washed and harvested with a PBS medium. They were centrifuged (140 *g*, 10 min, +4 °C) and then homogenized with a Polytron in the ice-cold binding buffer (Na_2HPO_4/KH_2PO_4, c = 50 mmol/L, pH = 7.5). The homogenate was centrifuged (23 000 *g*, 30 min, +4 °C) and the pellet obtained resuspended in the binding buffer to constitute the membrane preparation used for the binding assays. Aliquots of the membrane suspension (5–15 μg protein) were incubated for 60 min at 25 °C with [^{125}I]iodoproxyfan (c = 25 pmol/L) alone, or together with competing drugs dissolved in the same buffer to give a final volume of 200 μL. Incubations were performed in triplicate and stopped by four additions (5 mL) of ice-cold medium, followed by rapid filtration through glass microfiber filters (GF/B Whatman, Clifton, NJ) presoaked in polyethylene imine (ω = 0.3%). Radioactivity trapped on the filters was measured with a LKB (Rockville, MD) gamma counter (efficiency: 82%). Specific binding was defined as that inhibited by imetit (c = 1 μmol/L), a specific H_3 receptor agonist.[43] K_i values were determined according to the Cheng-Prusoff equation.[42] Data are presented as the mean of experiments performed at least in triplicate.

Computational methods

In order to elucidate the mode of interaction of the developed compounds at a molecular level, docking studies were carried out. Since the inhibitory activity data used in the present study were measured on the rat HMT it was preferable to perform our docking studies on this enzyme. For this purpose we generated a homology model of the rat HMT on the basis of the very recently published X-ray structure of human HMT.[23] The amino acid sequence of the rat HMT shows an overall identity of 84% compared to the human enzyme. The crystal structure of human HMT in complex with *S*-adenosylhomocysteine and the inhibitor quinacrine (1jqe) was retrieved from the Protein Database.[44] Chain B of 1jqe was used for modelling the rat enzyme. Sequence alignment and comparative protein modelling were performed using the BIOPOLYMER module within SYBYL 6.6.[45] To model amino acid substitutions the SCWRL side chain rotamer library was used.[46] The model refinement was carried out in a stepwise manner using the AMBER4.1[47] all atom force field and Kollman charges as implemented in SYBYL. The whole molecule was first subjected to a minimization keeping all protein back-bone atoms at fixed positions. Finally, the model was minimized until convergence, defined as an energy gradient of 0.05 kcal mol^{-1} $Å^{-1}$. The final rat HMT model was checked by the program PROCHECK[48] to verify its stereochemical quality.

The HMT inhibitor molecules were modelled in their mono-protonated form using the SYBYL TRIPOS force field. Computational docking was performed using the automated docking method AutoDock.[49] First, the grid maps were calculated using the C, H, O, N, and Cl atoms as the probe atoms within a three-dimensional grid centred on the binding pocket. Then, the ligands were docked subsequently into the binding pocket of HMT. Finally, the complex models were optimized by energy minimization using the YETI force field[50] until an energy gradient of less than 0.05 kcal,mol^{-1}, $Å^{-1}$ was reached. For each inhibitor, the complex showing the most favorable interaction energy was selected for further visual inspection and comparison.

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